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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/646,308	08/21/2003	Paul B. J. Burton	3432-US-NP	9578

22932 7590 11/09/2010

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EXAMINER	
JIANG, DONG	
ART UNIT	**PAPER NUMBER**
1646	

MAIL DATE	DELIVERY MODE
11/09/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/646,308	BURTON ET AL.	
	Examiner	Art Unit	
	DONG JIANG	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 August 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *46-49,51,52 and 64-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *46-49,51,52 and 64-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/18/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Applicant's response filed on 17 August 2010 is acknowledged and entered.

Currently, claims 46-49, 51, 52 and 64-67 are pending and under consideration.

Rejections Over Prior Art:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 46-49, 51, 52 and 64-67 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Waelti (US2004/0028687) and Yudestad et al. (Cardiovasc Res., 2002 Apr; 54(1):175-82, provided by applicants), and in view of Goodwin et al. (US5,674,704, provided by applicants), for the reasons of record set forth in the previous Office Actions mailed on 5/13/09 and 2/17/10.

Applicants argument filed on 17 August 2010 has been fully considered, but is not deemed persuasive for the reasons below.

At page 5 of the response, applicants maintain the argument set forth in the previous responses that, regarding the Yndestad reference, Yndestad found that 4-1BBL was one of 34

upregulated genes found in the peripheral blood mononuclear cells (PBMC) from chronic heart failure patients but not healthy blood donors (abstract page 175), and Yndestad's study did not result in the identification of any single factor correlating to chronic heart failure, thus, it would not have been obvious from this reference that antagonizing 4-1BB in partfcular, and 4-1BB alone, would provide a reduction of chronic cardiotoxicity caused by a chemotherapeutic agent. This argument is not persuasive because there is nothing unusual that Yndestad's study did not result in the identification of any single factor correlating to chronic heart failure as most diseases/disorders are associated with multiple factors. Further, while Yndestad found, including 4-1BBL, 34 upregulated genes in heart failure patients, the reference also emphasizes "in particular several members of the tumor necrosis factor (TNF) superfamily" (4-lBB ligand, APRIL, CD27L, CD40L, FasL, LIGHT, TRAIL-receptor 4 were upregulated); and "[I]n particular, the enhanced expression of several ligands in the TNF superfamily may reflect a potential pathogenic role of these cytokines in CHF" (abstract, for example). Clearly, in the Yndestad reference, the focus was given to a few members of TNF superfamily that were upregulated for their pathological role in CHF. Applicants further argue, as did in the preious responses, that according to Ynedstad, although 4-1BBL was one of the 34 upregulated genes, 4-1BBL was not considered to be "significantly upregulated", as stated on page 175, (abstract) "quantitative KT-PCR confirmed significantly upregulated gene expression of APRIL, LIGHT, FasL and CD27L" (page 175, abstract) (but not 4-1BBL) in CHF patents. This argument is not persuasive for the reasons of record. Nowhere in the Ynedstad reference has it stated that 4-1BBL was not significantly upregulated. In contrast, the reference clearly states "4-lBB ligand, APRIL, CD27L, CD40L, FasL, LIGHT, TRAIL-receptor 4 were upregulated".

At pages 5-6 of the response, applicants repeatedly argue that the authors (of the Ynedstad reference) stated "we have pinpointed several potentially interesting genes and gene families in the cytokine network that should be further investigated for their possible pathogenic role in this disorder, in particular, we found a marked upregulation of several ligands in the TNF superfamily as demonstrated by both cDNA expression arrays and real-time quantitative RT-PCR methods", clearly, the authors do attach significance to the fact that the upregulation of 4-1BBL and CD40L "were not verified" by RT-PCR, thus the low hybridization signals related to low abundance of transcripts for 4-1BBL and CD40L did not merely mean technical difficultly,

but dearly was interpreted as being less significant than the "marked upregulation" of other TNF ligands. This argument is not persuasive for the reasons of record. Ynedstad merely states "we failed to confirm the differential gene expression of 4-1BBL and CD40L" (page 179, 2nd column, 1st paragraph), which is not to say that 4-1BBL expression was not significant in CHF, which is applicants own interpretation, especially given the fact that the reference clearly states 4-lBB ligand, APRIL, CD27L, CD40L, FasL, LIGHT, TRAIL-receptor 4 were upregulated". Further, the elevated 4-1BBL expression in CHF patients *was demonstrated* in cDNA expression array hybridization assay that the expression of 4-1BBL, among other members of the TNF superfamily ligands, APRIL, CD27L, CD40L, FasL and LIGHT, was upregulated in the CHF group (page 179, 1st column, 2nd paragraph; and page 178, Table 3). Furthermore, even if 4-1BBL expression were less elevated comparing to other four members that were upregulated, it does not diminish the indication that 4-1BBL was involved in the pathology of CHF.

At page 6 of the response, applicants repeatedly argue that the authors noted that "receptors for APRIL, FasL, LIGHT, TNEa, and TRAIL have been reported to be expressed in the heart" (page 180, section 4.3) but not 4-1BB, and no mention is made of 4-1BB or 4-1BBL in the discussion of potential pathological implications in section 4.3, pages 180-181 although other TNF superfamily ligands are discussed. This argument is not persuasive because 4-1BB cannot be ruled out simply because it is not expressed in the heart as there is no logic or necessary connection that factors associated with heart failure have to be expressed in the heart. For example, the primary cause of CHF due to hypertension is not related to the heart. Further, while no mention is made of 4-1BB or 4-1BBL in the discussion in section 4.3, pages 180-181 in the Ynedstad reference, 4-lBB ligand is clearly mentioned in other places in the reference: it is demonstrated in cDNA expression array hybridization assay that the expression of 4-1BBL, among other members of the TNF superfamily ligands, APRIL, CD27L, CD40L, FasL and LIGHT, was upregulated in the CHF group (page 179, 1st column, 2nd paragraph; and page 178, Table 3); and in the abstract (which is the summary of the findings of the study): "4-lBB ligand, APRIL, CD27L, CD40L, FasL, LIGHT, TRAIL-receptor 4 were upregulated". Therefore, applicants argument that the upregulated 4-lBB ligand expression in CHF patients is insignificant is not persuasive.

Conclusion:

No claim is allowed.

Advisory Information:

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication should be directed to Dong Jiang whose telephone number is 571-272-0872. The examiner can normally be reached on Monday - Friday from 9:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Dong Jiang/
Primary Examiner, Art Unit 1646
11/6/10